Evidence-based recommendations for analgesic efficacy to treat pain of endodontic origin

A systematic review of randomized controlled trials

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ABSTRACT

Background. The purpose of this investigation was to identify evidence-based clinical trials to aid dental clinicians in establishing the efficacy for recommending or prescribing analgesics for pain of endodontic origin.

Types of Studies Reviewed. The authors prepared and registered a protocol on PROSPERO and conducted electronic searches in MEDLINE, Scopus, the Cochrane Library, and ClinicalTrials.gov. In addition, the authors manually searched the bibliographies of all relevant articles, the gray literature, and textbooks for randomized controlled trials. Two authors selected the relevant articles independently. There were no disagreements between the authors.

Results. The authors analyzed 27 randomized, placebo-controlled trials. The authors divided the studies into 2 groups: preoperative and postoperative analgesic treatments. There was moderate evidence to support the use of steroids for patients with symptomatic irreversible pulpitis. Also, there was moderate evidence to support nonsteroidal anti-inflammatory drugs (NSAIDs) preoperatively or postoperatively to control pain of endodontic origin. When NSAIDs were not effective, a combination of NSAIDs with acetaminophen, tramadol, or an opioid appeared beneficial.

Conclusions and Practical Implications. NSAIDs should be considered as the drugs of choice to alleviate or minimize pain of endodontic origin if there are no contraindications for the patient to ingest an NSAID. In situations in which NSAIDs alone are not effective, the combination of an NSAID with acetaminophen or a centrally acting drug is recommended. Steroids appear effective in irreversible pulpitis.

Key Words. Endodontics; analgesics; pain; flare-ups; randomized controlled trials.

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Historically, extraction of impacted third molars has served as a viable pain model for evaluating analgesic efficacy.[1] Investigators using oral and maxillofacial surgical models predominately have evaluated young healthy patient populations with minimal preoperative pain or concomitant medically compromising conditions. Patients in need of endodontic treatment differ from those patients in several ways. First, the endodontic patient population is generally older with possibly more complicated medical histories.[2] Second, the endodontic population can have preoperative pulpal or periradicular infections, which could influence postoperative pain.[3] Thus, these 2 differences could confound the results of analgesic efficacy and analgesic requirements. Also, preexisting pulpal or periradicular pain and inflammation may result in neuroplastic changes in the spinal and medullary dorsal horn.[4] In animal studies, the peripheral nociceptive barrage from an inflamed pulp is sufficient to cause a 5-fold increase in dorsal horn neuron discharge rate,[5] up to a 3-fold increase in the size of the receptive field of A delta fibers,[6] and sprouting of nerve calcitonin gene-related peptide fibers in inflamed tissue surrounding sites of pulpal injury.[7] Essentially, these inflammatory mediators in pulpitis and periapical anatomy result in central and peripheral sensitization that could increase the severity of the patient's discomfort.[8]

Although various dental pain models possess some biological similarities, including elevated levels of key inflammatory mediators,[9-11] they are likely also dissimilar given the difference in stimulus (postsurgical

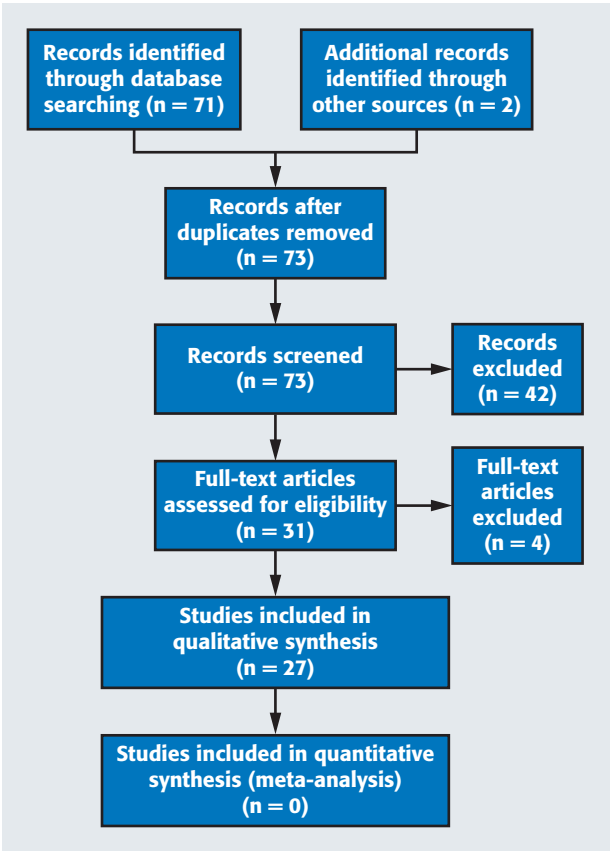

Figure. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart. *Source: Moher and colleagues.*[17]

conditions versus infection) and time (endodontic pain has much more time for accumulation of polymorphonuclear leukocytes,[12] mast cells,[13] macrophages,[12] T cells [thymus cells],[13] B cells [bone marrow–derived or bursa-derived cells],[12] neuronal sprouting,[7] and gene regulation[14,15]).

In the early phase of pulpitis, a cellular immunoresponse is induced by T lymphocytes; in the advanced phase, the B lymphocytes appear with the destruction of pulp tissue by proteolytic enzymes released from infiltrating neutrophils, mast cells, and macrophages.[12,13] In addition, peripheral and central sensitization occur as a result of hyperalgesia controlled by gene expression regulated by nerve growth factor.[14,15]

Thus, there was a need for a systematic review of the English-language peer-reviewed literature focusing on the evidence regarding pain of endodontic origin and analgesics used to decrease that pain. Because the potential benefits of pain reduction using analgesics always must be balanced against the potential adverse effects of those medications, the goal of this investigation was to report the best available scientific evidence regarding the efficacy of analgesics and corticosteroids to decrease endodontic preoperative and postoperative pain.

METHODS

We prepared and registered a protocol on PROSPERO (registration CRD42016035671) and conducted electronic searches on MEDLINE, Scopus, the Cochrane Library, and ClinicalTrials.gov using strict inclusion and exclusion criteria. We also searched the gray literature for randomized controlled trials (RCTs). We excluded non–English-language articles without English-language abstracts. Key search terms included *endodontics*, *root canal treatments*, *analgesics*, *randomized controlled clinical studies*, and *pain and/or flare-ups*. In addition, we manually searched the bibliographies of all relevant articles, the gray literature, and textbooks for RCTs. Two reviewers (A.A., J.C.K.) independently selected the relevant articles. In case of any disagreement, the authors would come together to discuss the divergence and then agree on the final outcome.

The inclusion criteria were as follows:

- RCTs published in peer-reviewed, English-language journals from January 1990 through April 2016 in which the authors investigated reduction of pain or flare-ups due to use of analgesics;
- the comparison between patients undergoing endodontic therapy with analgesics and those without analgesics or patients receiving placebo was measured for pain reduction;
- the sample size in the study was identified;
- the effect of pain reduction as a primary objective was measured.

Exclusion criteria consisted of studies that did not meet these inclusion criteria or were animal or laboratory studies.

We used the Assessing the Methodological Quality of Systematic Reviews checklist, the Oxford Systematic Review Appraisal Sheet, the Critical Appraisal Skills Programme, and the Grading of Recommendations Assessment, Development and Evaluation system for grading evidence to ensure the accuracy of this data analysis in this systematic review.[16-19] We used the Cochrane Collaboration's risk of bias tool to assess the methodological quality of the included studies.[20]

RESULTS

Because of the variety of research methodologies, clinical diagnoses, and analgesic regimens, it was not possible to

ABBREVIATION KEY. **AB:** Attrition bias. **DM:** Double masked. **LSS:** Low sample size. **NSAID:** Nonsteroidal anti-inflammatory agent. **NSET:** Nonsurgical endodontic treatment. **PA:** Periapical. **RCT:** Randomized controlled trial. **RSG:** Random sequence generation. **SR:** Selective reporting.